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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/22

A1

(11) International Publication Number: **WO 97/42945**

(43) International Publication Date: 20 November 1997 (20.11.97)

(21) International Application Number: PCT/EP97/02418

(22) International Filing Date: 12 May 1997 (12.05.97)

(30) Priority Data:
96810301.0 13 May 1996 (13.05.96) EP
(34) Countries for which the regional or international application was filed: DE et al.

(71) Applicant *(for all designated States except US)*: NOVARTIS CONSUMER HEALTH S.A. [CH/CH]; Route de l'Etraz, CH-1260 Nyon (CH).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SCHMID, Beat [CH/CH]; Le Jordil, CH-1173 Féchy (CH).

(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS

(57) Abstract

Pharmaceutical compositions for oral administration comprising menthyl lactate are disclosed. They are useful in the treatment of e.g. acute or chronic diseases of the upper or lower respiratory tract, in particular common cold, rhinitis or sinusitis. Furthermore, the invention concerns a method of treating acute or chronic diseases of the upper or lower respiratory tract which method comprises orally administering to a mammal including man a therapeutically effective amount of menthyl lactate. Further, the invention relates to the use of menthyl lactate for the manufacture of a pharmaceutical composition adapted to oral administration for the treatment of acute or chronic diseases of the upper or lower respiratory tract.

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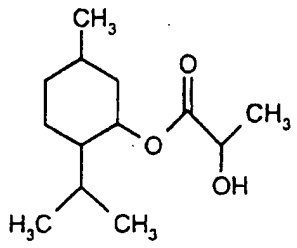
Oral pharmaceutical compositions

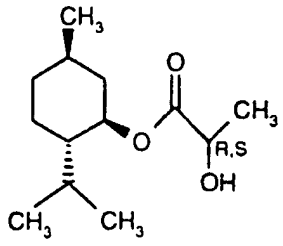
The invention relates to pharmaceutical compositions adapted to oral administration comprising a certain menthyl ester and to the use of the latter for the manufacture of a pharmaceutical composition.

Thus, the invention relates to a pharmaceutical composition adapted to oral administration comprising menthyl lactate together with at least one pharmaceutically acceptable carrier.

The structural formula of menthyl lactate is as follows:



As the compound contains 4 asymmetric carbon atoms, there are existing 16 different stereoisomers. The term "menthyl lactate" is intended to cover each of these stereoisomers as well as any racemates and any other mixtures of these stereoisomers. Preferred is the racemate of the following structure



which is derived from the naturally occuring (-)-menthol. This compound is available commercially e.g. under the name "FRESCOLAT, Type ML" from Haarmann & Reimer GmbH (Germany). It can also be readily made by processes known in the art by esterifiying the hydroxy group of menthol with lactic acid.

Menthyl lactate is very well suited for oral administration because it is odorless and does not have any unpleasant taste.

The oral pharmaceutical compositions of the invention have valuable pharmacological properties. Especially they are beneficial in the treatment of acute or chronic diseases of the upper or lower respiratory tract, for example common cold, rhinitis or sinusitis, but also e.g. bronchitis or asthma.

The beneficial properties of menthyl lactate can be demonstrated, for example, in the following tests.

The inhibition of inflammatory mediators in monocytes may be demonstrated, for example, in the carrageenin induced paw edema test in the rat [see C. Winter et al., Proc. Soc. Exp. Biol. Med. 111 (1962) 544-547].

The reduction of spontaneous tone in the guinea pig trachea can be demonstrated, for example, according to the test described in M. Wasserman et al., Eur. J. Pharmacol. 46 (1977) 303.

Expectorant activity can be demonstrated, for example, in the mouse according to the test described by H. Enger and I. Szelenyi in: The Pharmacological Methods, Elsevier Science Publishing Co., New York 1984, page 151.

The dosage of the active ingredient may depend on various factors, such as warm-blooded species, sex, age, weight and individual condition of the warm-blooded animal.

Normally the daily dosage which is administered to a warm-blooded animal weighing approximately 75 kg is from 0.4 up to 15 mg/kg, especially from 1 up to 7 mg/kg. This dose may be taken once daily or, if desired, also in several, optionally equal, partial doses.

"mg/kg" means mg drug per kg body weight of the mammal - including man - to be treated.

The pharmaceutical compositions of the invention in single dose unit form typically contain of from about 1% up to about 90%, preferably of from about 6% up to about 90%, more preferably of from about 8% up to about 85%, most preferably of from about 10% up to about 70% and especially of from about 10% up to about 50%, and formulations not in single dose unit form typically contain of from about 0.1% up to about 40% of the active ingredient (menthyl lactate). All percentages given are percentages by weight, if not indicated otherwise. Single dose unit forms such as capsules, tablets, dragées or sachets contain e.g. from about 20 up to about 1000 mg, especially from 50 up to 500 mg, of the active ingredient.

Pharmaceutical compositions for oral administration are, for example, compositions in single dose unit forms, such as dragées, tablets or capsules. Moreover, sachets filled with the active substance in powder or granule form come into consideration. All these pharmaceutical compositions are prepared in a manner known *per se*, for example by means of conventional mixing, granulating or confectioning processes. For example, they can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granules, after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablet cores, enteric coated tablet capsules or pellets, tablets and capsules may be provided with suitable, optionally enteric, coatings or coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate or aqueous coatings, such as Eudragit® L30D. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise

gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further pharmaceutical compositions to be administered orally and being in single dose unit form are e.g. hard gelatin capsules made of gelatin, and soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

Other oral dosage forms not being in single dose unit form, are, for example, syrups, liquid suspensions or solutions. They are prepared in customary manner. As already mentioned above, they typically contain menthyl lactate in an amount of from about 0.1% up to about 40%, preferably of from about 6% up to about 40%, more preferably of from about 6% up to about 20%; or of from about 1% up to about 20%; and especially of from about 10% up to about 20%, of the total composition.

Syrups, for example, comprise the active ingredient e.g. in suspended form and in a concentration of approximately from 1 to 20 %, preferably from 1 to 5 %, or in a concentration that provides a suitable single dose when administered e.g. in a measure of 5 or 10 ml.

Another embodiment of the invention is characterized by the pharmaceutical compositions as disclosed but which do not contain thymol.

The invention further relates to the use of menthyl lactate for the manufacture of a pharmaceutical composition adapted to oral administration for the treatment of acute or

chronic diseases of the upper or lower respiratory tract, in particular common cold, rhinitis or sinusitis but also e.g. bronchitis or asthma, in mammals including man.

Moreover, the invention relates to a method of treating acute or chronic diseases of the upper or lower respiratory tract, in particular common cold, rhinitis or sinusitis but also e.g. bronchitis or asthma, which comprises orally administering to a mammal in need of such treatment a therapeutically effective amount of menthyl lactate.

The following examples are intended to exemplify but not to limit the invention.

Example 1: Soft capsules: 5000 soft gelatin capsules, each comprising 50 mg of the active ingredient, menthyl lactate, are prepared as follows.

Composition (for 5 000 casules)

active ingredient	250 g
Lauroglycol®	2 l

Preparation process: The active ingredient is suspended in Lauroglycol® (= propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground to a particle size of approximately from 1 to 3 µm in a wet pulveriser. 419 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 2: Soft capsules: 5000 soft gelatin capsules, each comprising 50 mg of the active ingredient, menthyl lactate, are prepared as follows.

Composition (for 5 000 casules)

active ingredient	250 g
PEG 400	1 l
Tween 80®	1 l

Preparation process: The active ingredient is suspended in PEG 400 (= polyethylene glycol with M_r from approximately 380 to approximately 420, Fluka, Switzerland) and Tween 80® (= polyoxyethylene sorbitan monolaurate, Atlas Chem. Ind., Inc., USA, supplied by Fluka,

Switzerland) and is ground to a particle size of approximately from 1 to 3 µm in a wet pulverizer. 430 mg portions of the mixture are then introduced into soft gelatin capsules by means of a capsule-filling machine.

Example 3: Dry-fill capsules: 5000 capsules, each comprising 250 mg of the active ingredient, menthyl lactate, are prepared as follows.

Composition (for 5000 capsules)

active ingredient	1250 g
talcum	180 g
wheat starch	120 g
magnesium stearate	20 g
lactose	80 g

Preparation process: The powdered substances mentioned are pressed through a sieve having a mesh size of 0.6 mm. 330 mg portions of the mixture are introduced into gelatin capsules by means of a capsule-filling machine.

Example 4: Hard gelatin capsules containing 500 mg of the active ingredient, menthyl lactate, are prepared as follows.

Composition (for 1000 capsules)

active ingredient	500 g
lactose	250 g
microcrystalline cellulose	30 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

Preparation process: The sodium lauryl sulfate is added through a sieve of 0.2 mesh size to the lyophilised active ingredient. The two components are intimately mixed. First the lactose is added through a sieve of 0.6 mm mesh width,and then the microcrystalline cellulose is added through a sieve of 0.9 mm mesh width. The mixture is again intimately mixed for 10 min. Finally, the magnesium stearate s added through a sieve of 0.8 mm mesh width. After

stirring for a further 3 min, 790 mg portions of the resulting formulation are introduced into hard gelatin capsules of suitable size.

Example 5: Syrup containing 1% of the active ingredient, menthyl lactate, is prepared as follows.

42 g p-hydroxybenzoic acid methyl ester, 18 g p-hydroxybenzoic acid n-propyl ester and - under warming - 100 g of the active ingredient are dissolved in 3 l of distilled water. 1.5 l glycerin, 4 l of 70 % sorbit solution, 1000g of crystalline saccharose, 350 g of glucose and fragrance, e.g. 250 g of "Orange Peel Soluble Fluid" (Eli Lilly, Indianapolis, USA) or 5 g of natural lemon fragrance and 5 g of "Halb und Halb" essence (both of Haarmann and Reimer, Holzminden, Germany), are added, the solution obtained is filtered, and the filtrate is filled up to 10 l with distilled water.

Claims

1. A pharmaceutical composition adapted to oral administration comprising menthyl lactate together with at least one pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1 for use in the treatment of acute or chronic diseases of the upper or lower respiratory tract.

3. A pharmaceutical composition according to claim 1, which is in single dose unit form and comprises menthyl lactate in an amount of from about 1 up to about 90 weight-% of the total composition.

4. A pharmaceutical composition according to claim 2, which is in single dose unit form and comprises menthyl lactate in an amount of from about 1 up to about 90 weight-% of the total composition.

5. A pharmaceutical composition according to claim 1 or claim 2, which is in single dose unit form and comprises menthyl lactate in an amount of from about 6 up to about 90 weight-% of the total composition.

6. A pharmaceutical composition according to claim 1 or claim 2, which is in single dose unit form and comprises menthyl lactate in an amount of from about 10 up to about 70 weight-% of the total composition.

7. A pharmaceutical composition according to claim 1 or claim 2, which is in single dose unit form and comprises menthyl lactate in an amount of from about 10 up to about 50 weight-% of the total composition.

8. A pharmaceutical composition according to any one of claims 1-7, which is in single dose unit form and comprises menthyl lactate in an amount of from 20 mg up to 1000 mg.

9. A pharmaceutical composition according to any one of claims 1-7, which is in single dose unit form and comprises menthyl lactate in an amount of from 50 mg up to 500 mg.

10. A pharmaceutical composition according to claim 1 or claim 2, which is in the form of a syrup, a liquid suspension or a solution, which comprises menthyl lactate in an amount of from about 0.1 up to about 40 weight-% of the total composition.

11. A pharmaceutical composition according to claim 1 or claim 2, which is in the form of a syrup, a liquid suspension or a solution, which comprises menthyl lactate in an amount of from about 0.1 up to about 40 weight-% of the total composition, and which does not contain thymol.

12. A pharmaceutical composition according to claim 10 or claim 11, which comprises menthyl lactate in an amount of from about 6 up to about 40 weight-% of the total composition.

13. A pharmaceutical composition according to claim 10 or claim 11, which comprises menthyl lactate in an amount of from about 6 up to about 20 weight-% of the total composition.

14. Use of menthyl lactate for the manufacture of a pharmaceutical composition adapted to oral administration for the treatment of acute or chronic diseases of the upper or lower respiratory tract in mammals including man.

15. A method of treating acute or chronic diseases of the upper or lower respiratory tract, which comprises orally administering to a mammal in need of such treatment a therapeutically effective amount of menthyl lactate.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/02418

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07477 A (WARNER-LAMBERT COMPANY) 14 April 1994 see the whole document ---	1-15
X	DE 26 08 226 A (HAARMANN & REIMER GMBH) 8 September 1977 see the whole document ---	1-15
X	FR 2 630 004 A (AMERICAM CYANAMID COMPANY) 20 October 1989 see page 10 -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1997	01.09.97

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/EP 97/02418

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 15
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter al Application No
PCT/EP 97/02418

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9407477 A	14-04-94	AU 5298493 A	26-04-94
		ZA 9307353 A	29-04-94
DE 2608226 A	08-09-77	FR 2342057 A	23-09-77
		JP 52105223 A	03-09-77
		NL 7702074 A	30-08-77
FR 2630004 A	20-10-89	US 4929446 A	29-05-90
		AU 616504 B	31-10-91
		AU 3313889 A	26-10-89